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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,892	03/26/2001	George Gow Brownlee	P02074US0	5755

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,892	BROWNLEE ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-19,22-40 and 51-79* is/are pending in the application.

4a) Of the above claim(s) *26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-19, 22-25, 28-40, 51-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed June 8, 2005 in response to the Office Action of March 8, 2005 is acknowledged and has been entered. Claims 61-79 have been added. Claims 13-19, 22-25, 28-40, 51-79 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 101

The rejection of claims 1-25, 28-40 and 48-60 under 35 U.S.C. 101 because the attenuated virus reads on a virus that can occur in nature wherein the virus is less virulent that another strain **is withdrawn** in view of applicants amendment to the claims indicating that the nucleic acid has been isolated.

Claim Rejections - 35 USC § 112

The rejection of claims 1-25, 28-40 and 48-56 under 35 U.S.C. 112, first paragraph, **is withdrawn** in view of applicants amendments to the claims deleting the phrase and "function modification thereof" from the claim.

Claim Rejections - 35 USC § 102

The rejection of claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 under 35 U.S.C. 102(e) as being anticipated by Palese et al. (U.S. Pat. No. 6,022,726) **is withdrawn** in view of applicants amendment to the claims indicating that the nucleic acid requires a modification in the base pair

at position 11' from the 3' end and 12' from the 5' end or at position 10' from the 3' end and 11' from the 5'.

The rejection of claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Palese P. (WO 93/21306) **is withdrawn** in view of applicants amendment to the claims indicating that the nucleic acid requires a modification in the base pair at position 11' from the 3' end and 12' from the 5' end or at position 10' from the 3' end and 11' from the 5'.

The rejection of claims 1-5, 8, 9, 12-18, 20-24, 28, 29, 33 and 37 under 35 U.S.C. 102(b) as being anticipated by Bergmann et al. (Journal of General Virology, 1995, see IDS) **is withdrawn** in view of applicants amendment to the claims indicating that the nucleic acid requires a modification in the base pair at position 11' from the 3' end and 12' from the 5' end or at position 10' from the 3' end and 11' from the 5'.

Claim Rejections - 35 USC § 103

The rejection of claims 1-25, 28-40 and 48-60 under 35 U.S.C. 103(a) as being unpatentable over Bergmann et al. (Journal of General Virology, 1995) [Berg1], Bergmann et al. (Virus Research, 1996) [Berg2] and Kim et al. (Journal of General Virology, 1997) in view of Castrucci et al. (Journal of Virology, 1992) **is maintained** for reasons of record.

Applicants arguments submitted June 9, 2005 have been fully considered but fail to persuade. The instant claims are drawn to a virus comprising genomic RNA having mutaions in

the duplex region requiring a modification in the base pair at position 11' from the 3' end and 12' from the 5' end or at position 10' from the 3' end and 11' from the 5'. Claims 30, 31, 34, 35, 65, 66 make reference to specific mutations or "functionally equivalent substitutions at the same position." "Functionally equivalent substitutions at the same position" for purposes of the instant rejection is interpreted to be a mutation that results in attenuation.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case applicants are arguing the references separately in that the Bergman reference is directed to the production of a chimeric virus and that the reference does not show the specific mutations which are now claimed. Applicants argue that the Office has not made a distinction between a chimeric virus and a mutated virus. In this instance neither of the Bergman references Berg1 and Berg2 discuss creating chimeric viruses they both refer to the new viruses as mutants. "The nature of a chimera is that it effectively combines two portions of known strains together" (Applicants

response page 15). Berg1 and Berg2 both make mutant viruses and the mutations are introduced using the ribonucleoprotein transfection method (see Berg1 figure 1, page 3212 column 1). The mutations were introduced in influenza A and only point mutations were made in the promoter region of influenza A to make the promoter look like the sequence of an influenza B promoter. Berg2 the title alone indicates that the reference is contemplating viral mutation and not chimeras. The title of Berg 2 reads "mutations in the nonconserved noncoding sequences of the influenza virus segments affect vRNA formation." Applicants' arguments are not convincing since it is clear from the references that these products are considered mutants.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Berg1 and Berg 2 references discuss that changes in the promoter of influenza A virus leads to changes in the viral phenotype in tissue culture and in the animal. Thus the Berg1 and Berg2 references correlate what is observed in the test tube with what is expected in the animal or in tissue culture.

Applicants also argue that Berg1 and Berg2 introduce a number of chances and thus it would not be possible to establish which mutations are useful. This argument is not convincing because the Berg1 and Berg2 references indicate that making a single change in the promoter NA/X results in an attenuated phenotype and making 3 base pair changes in the promoter region

also results in an attenuated phenotype. Thus the references establish the regions in which mutations are effective at attenuating the phenotype. Kim et al. teaches the effect of mutations in the influenza promoter to the production of CAT in the test system. Kim et al. teaches that changes in the promoter results in reduced activity compared to wild type (see Kim et al. page 355, figure 2). This mutation information can then be generalized to the effect the mutations would have on the whole virus in tissue culture or in an animal especially when considering the observed correlation in the Berg1 and Berg2 references.

Berg1 teaches the construction of two influenza A virus that have mutations in the non-coding sequences (see figure 1) NA/X and NA/Y. NA/X and NA/Y both have reduced genomic RNA in infected cells (see figure 3), the RNA reduction was 5-7 fold for NA/Y and 3 fold for NA/X. The reference teaches that the reduction in expression of one viral segment in a cell correlates with an attenuated viral phenotype in tissue culture and in the animal. The reference does not teach the specific mutations base pair at position 11' from the 3' end and 12' from the 5' end or at position 10' from the 3' end and 11' from the 5'.

Applicants argue that the position of the polyadenylation signal and length of the promoter is important replication efficiency is influenced by the number of nucleotides being transcribed. Applicants refer to several reference in making the arguments. The references have not been cited on an IDS form 1449 or on an 892 form, thus the references have not been considered on the merits. Additionally, without the references their augments cannot be fully addressed.

It is known in the art that other regions of the influenza virus also contribute to an attenuated phenotype Catrucuccie et al. teaches that addition of foreign epitopes into the

neuramidase gene contribute to attenuation of the virus. Thus the argument that other regions or even the length of the promoter may have an effect on attenuation is not convincing in the instant rejection which is drawn to the combination of references indicating that it would have been obvious to make mutations in the influenza virus promoter in order to achieve an attenuated phenotype.

Berg2 teaches two influenza A/WSN/33 mutant viruses that have changes in the non-coding region of the 5' and 3' ends (see figure 1). The reference analyzed the effect of these mutation on the vRNA production in infected cells (see page 29, section 3.6). The NA/1+2 was almost 100 fold reduced as compared to the wild type virus and the partial revertants were slightly reduced. The reference teaches that the reductions in the viral titers correlate with the vRNA patterns in the cell. The reference does not teach mutations at position 11 and 10 from the 3' terminus or at position 11 and 12 from the 5' terminus.

Kim et al. teach mutations in the influenza A virus non-coding region and assays the ability to express CAT activity comparative to wild type. The reference teaches mutation in the 10-11' region of the 3' end and the 11-12' region of the 5' end (see figure 2). Mutant #24 (see figure 2) has 3 base pair mutations at portions 10-12 from the 3' and 11-13 from 5'. The mutations are assayed for their ability to express the protein product all mutation were found to express protein at a lower level compared to wild type. The reference does not teach the correlation of reduced protein expression with an attenuated phenotype.

Castrucci et al. teach that insertion of a heterologous sequence into the neuramidase gene of influenza virus results in the attenuation of the viral construct.

It would have been obvious to on of ordinary skill in the art at the time the inventions was made to utilize the mutations that Kim et al. has shown to be effective at reducing the expression of a protein coding sequence using mutations in the promoter to produce an attenuated virus as taught by either Bergmannn reference. One having ordinary skill in the art of molecular biology would have had a high expectation of success in applying the Kim et al. mutations because the art as shown in Bergmann et al. that reduced promoter activity correlates with a reduction in protein production which results in an attenuated phenotype of the virus. Adding an additional heterologous sequence into the attenuate influenza construct would be an obvious step to create a virus that exhibits an even greater attenuated phenotype. The art already has taught that insertion of a heterologous sequence into the influenza neuramidase gene will result in an attenuated phenotype. Therefore, the instant invention is obvious over both Bergmann et al. references and Kim et al. in view of Castrucci et al.

Double Patenting

The rejection of claims 1-5, 8-24, 28, 29, 33, 37-39 and 48-60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,022,726 **is withdrawn** in view of applicants amendment to the claims indicating that the nucleic acid requires a modification in the base pair at position 11' from the 3' end and 12' from the 5' end or at position 10' from the 3' end and 11' from the 5'.

Conclusion

No claims allowed.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 8/18/05